

IND [REDACTED]

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IND [REDACTED]

**Review and Evaluation of
Pharmacology and Toxicology Data
Division of Dermatologic and
Dental Drug Products (HFD-540)**

Norman A. See, Ph.D., R.Ph.
Draft Completed: 3/29/96
Revised: 4/3/96

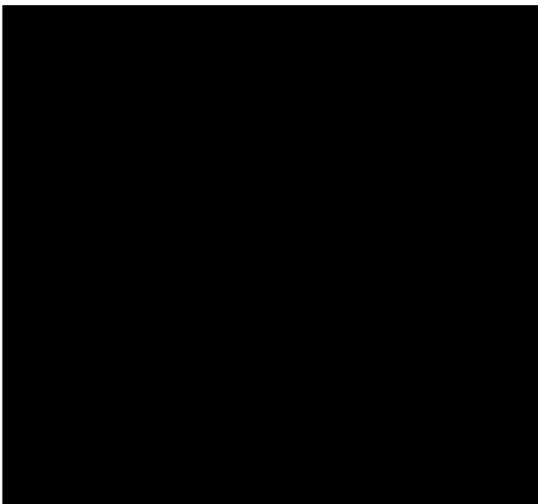
Original IND Summary

Submission number	Submission Date	Center Receipt Date
000	1/30/96	1/31/96
001, RD, IT	2/21/96	2/26/96

Sponsor: Bone Care International

Drug: 1-alpha-hydroxyvitamin D₂; 1a-OH-D₂; secoergosta-5,7,10(19),22-tetraen-1,3-diol, (1a,3B,5Z,7E,22E)

Structure:



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Related Drugs/INDs/NDAs: IND [REDACTED] was submitted by the same sponsor for the same drug, but for the treatment of osteoporosis (submitted to HFD-510).

Background Information: The test material is a synthetic vitamin D analog (1a-OH-D₂). 1a-OH-D₂ is a prodrug, being converted to 1a, 25-(OH)₂-D₂ in the liver. The rationale behind the use of a vitamin D analog in the treatment of psoriasis is that psoriasis involves increased keratinocyte proliferation, and vitamin D inhibits keratinocyte division.

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Clinical Protocol(s): A clinical study has been proposed that would involve up to 20 subjects. The subjects would be between the ages of 18 and 70 and present with moderate chronic plaque-type psoriasis. Exclusion criteria would include women that were pregnant or nursing, patients with a baseline urine calcium level above 3.7mmol/24-hours, and patients with chronic hypercalcemia or renal impairment. The patients would receive treatment for a minimum of 8 weeks; at the discretion of the investigator, the treatment period might be extended up to a maximum of 20 weeks for a given patient. Treatment would consist of oral administration of 4mg (four 1mg capsules) of 1a-OH-D₂ daily before breakfast. The subjects will be monitored after 1, 2, 4, and 8 weeks of treatment (and at 4 week intervals thereafter if treatment is continued) for changes in the concentration of calcium in the blood and/or an increase in the rate of calcium loss in the urine. If the serum calcium rises above the upper limit of the normal range, the patient will be instructed to decrease the dosage to 3mg 1a-OH-D₂ per day. Treatment would be discontinued if the serum calcium rose 0.2mmol/l above the upper limit of the normal range. The maximum exposure to 1a-OH-D₂ currently proposed under IND [REDACTED] is 4mg/day, which equates to 0.08mg/Kg/day in a 50kg patient (for up to 20 weeks).

Non-Clinical Information Supporting the Safety of the Proposed Clinical Protocol(s): Note: The nonclinical studies that Bone Care International has conducted with 1a-OH-D₂ have previously been submitted to IND [REDACTED], and were evaluated by the Division of Metabolic and Endocrine Drug Products (HFD-510). The initial submission to IND [REDACTED] referenced IND [REDACTED] in regard to these studies. Because documents that have been submitted to HFD-510 are not readily available (they are in the Parklawn building), I requested that the nonclinical studies be resubmitted to IND [REDACTED]. For the sake of expediency I will only re-review the chronic toxicology studies in this summary. Please see the Pharmacology reviews of IND [REDACTED] for reviews of the other nonclinical studies that were submitted. For convenience, the entire list of studies that were submitted is presented below; the studies that will be reviewed in this summary are indicated by an asterisk.

Studies Submitted in Amendment 001:

1. Biologic response to 1a-hydroxyvitamin D₂ in macaca fascicularis. Study No. 053.
2. Acute toxicity study of [REDACTED] 870 in mice. Study No. 1291/AC.
3. Acute toxicity study in rats. Study No. 615-001.
4. Acute intraperitoneal toxicity study of [REDACTED] 870 in rats. Study No. 1292/AC.
5. Four-week comparative toxicity study of [REDACTED] 870 and 1a-OH-D₃ via oral gavage in rats. Study Nos. 1224/SU and 5651/SU.
6. Effect of BCI-101 on serum biochemistry in rats. Study No. [REDACTED] 464-BCI-001-91
7. 13-week oral toxicity study in rats. Study No. 615-002.
8. * 52-week oral toxicity study in rats. Study No. 295-136.
9. Two-week oral toxicity study of [REDACTED] 870 in cynomolgus monkeys. Study No. 5458/SU.
10. 13-week oral toxicity study in cynomolgus monkeys. Study No. 615-004.
11. * 52-week oral toxicity study in monkeys. Study No. 295-135.

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12. 4-week oral range finding study of [REDACTED]-870 in mice. Study No. 1293/CA.
 13. Bacterial mutagenicity study of [REDACTED]-870. Study No. 58/MH.
 14. Micronucleus test of [REDACTED]-870 in mice. Study No. 1133/GE.
 15. Segment I reproduction study of [REDACTED]-870 in rats. Study No. 1146/FE.

Note: An Ames test and a micronucleus test conducted with 1a-OH-D₂ both yielded negative results, suggesting that the compound is not mutagenic. In a male and female fertility and reproductive-performance study, no effect on reproductive parameters was observed at dosages up to 2.5mg/kg/day (the highest dose studied).

Review of nonclinical studies:

1. One-year oral toxicity study in rats with [REDACTED]-870, study No. 295-136, in-life 4/91-4/92, study report dated 3/31/93, conducted by [REDACTED] in compliance with Good Laboratory Practice regulations (21 CFR 58).

1a-OH-D₂ was dissolved in fractionated coconut oil and administered by gavage to groups of 35 [REDACTED] CrI CD rats of each sex in dosages of 0 (vehicle control), 0.02, 0.06, 0.55, and 5mg/kg/day for one year. The dosages used in this study are compared to the maximum currently proposed clinical dosage (4mg/day, or 0.08mg/Kg/day in a 50kg individual) below:

<u>Rat dose (mg/m²)</u>	<u>Multiple of</u>	<u>Multiple of</u>	<u>(mg/kg/day)</u>	<u>human dose (mg/kg)</u>	<u>human dose</u>
0.02	0.25	0.044			
0.06	0.75	0.13			
0.55	6.9	1.2			
5.0	62.5	11.0			

The parameters that were monitored included survival, clinical observations, body weight, food consumption, clinical pathology (blood chemistry, urinalysis, and hematology (including leukocyte differential)), ophthalmology, and gross pathology. Clinical pathology was performed on samples obtained from (only) 10 randomly selected animals per sex per group after 3, 6, and 12 months on-study; samples were obtained (as much as possible) from the same animals at each time point. Ten rats per sex per group were sacrificed after six months on-study. Blood samples were collected at 4, 8, and 24 hours after dosing from 10 rats/sex/group after six months on-study and from all surviving animals after 12 months on-study; these samples were analyzed to determine the plasma level of the test material. All major tissues were preserved. Histopathology was performed on all major tissues from animals that received 0 or 5mg/kg/day (control and high-dose groups), as well as all animals sacrificed *in extremis*. Additionally, sections of bone, bone marrow, spleen, liver, kidney, and heart were examined from all treatment groups.

Results:

Survival. Of 25 animals/sex/group originally scheduled for terminal sacrifice, survival after 52 weeks was:

<u>Dosage Level (mg/kg/day)</u>	<u>Number of Animals Surviving Until Week 52</u>	
	<u>Male</u>	<u>Female</u>
0 (control)	25	25
0.02	24	24
0.06	25	24
0.55	23	24

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Survival of the high-dose males ranged from 147 days to 369 days; only three high-dose males survived longer than day 257 (week 36). Median survival for high-dose males was approximately day 200. Of 35 high-dose males at the beginning of the study, 29 were eventually found dead, including the single high-dose male that survived until week 52. Survival of the high-dose females ranged from 160 days to 371 days (terminal sacrifice). Apparently, there were 11 high-dose females that received treatment for at least 360 days and that underwent necropsy and tissue fixation prior to the onset of autolysis (were not found dead), including four that are listed as dying on day 364 following blood collection. The cause of the deaths of the treated animals was not determined.

Clinical observations. Animals that eventually died (or were sacrificed *in extremis*) frequently exhibited hunched posture, decreased defecation, stained body surface, labored breathing, rales, decreased activity, and red/brown material around the nose. Similar signs were observed during weeks 40-52 in some animals at 0.55mg/kg/day. Labored breathing was also observed in 5 females at 0.06mg/kg/day around the end of the study.

Body weight. In males, body weight gain was slightly (but statistically significantly) increased at 0.06mg/kg/day, but decreased substantially at 0.55mg/kg/day and above. In females, body weight gain was slightly decreased at 0.55mg/kg/day and substantially decreased at 5.0mg/kg/day.

Food consumption. No remarkable observations.

Ophthalmology. No remarkable observations.

Blood chemistry. A trend toward elevated serum levels of calcium was apparent in both males and females at 0.55mg/kg/day and above. Plasma phosphorus was statistically significantly elevated in animals at 0.55mg/kg/day and above. Total protein and globulin were slightly reduced in high-dose males. High-dose females exhibited increased levels of alkaline phosphatase and aspartate aminotransferase.

Hematology. Erythrocyte parameters, including the concentrations of erythrocytes and hemoglobin and the hematocrit, tended to be decreased in both males and females at 0.55mg/kg/day and above. An increase in the concentration of reticulocytes was observed in both males and females at 0.55mg/kg/day and above. Although certain other parameters exhibited fluctuations, no clear trends were apparent.

Urinalysis. Urinary pH was decreased in both males and females at 0.55mg/kg/day and above. The rates of excretion of calcium and phosphorus were increased in both males and females at 0.55mg/kg/day and above.

Organ weights. Data from high-dose males were not available due to poor survival. Males at 0.55mg/kg/day exhibited a number of statistically significant differences from control in regard to mean organ weights that had been normalized to body weight; this was a result of reduced mean body weight in this group. No remarkable changes in mean absolute organ weight or in mean organ weights normalized to brain weight were observed, with the possible exception of a trend toward reduced mean liver weight.

Females at 0.06mg/kg/day exhibited reduced mean body weight, resulting in artifactual changes in organ-weight values following normalization to body weight. The means of the absolute weights of the kidney and the pituitary were increased in females at 0.55mg/kg/day and above. The mean absolute

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weight of the liver was decreased in females at 5mg/kg/day. These changes in mean absolute organ weights were apparently related to treatment.

Gross pathology. Treatment-related macroscopic changes were evident at 0.55mg/kg/day and above. Increased thickness of certain bones was observed, including the sternum and the vertebrae. Increased thickness of certain soft tissues was also observed, including the aorta, mesenteric blood vessels, and blood vessels in the serosa of the stomach. These effects tended to be more severe in males than in females. No remarkable macroscopic observations were made in animals that received 0.06mg/kg/day or less.

Histopathology. Note: Since routine histopathology of tissues other than the bone, bone marrow, spleen, liver, kidney, and heart were only performed on control and high-dose animals, and since survival of high-dose animals was extremely low, in effect this study did not include histopathologic examination (except for the bone, bone marrow, spleen, liver, kidney, and heart). Please see the "Reviewer's comment", below, for discussion of this omission.

Treatment-related microscopic changes in the bone, bone marrow, spleen, liver, kidney, and heart were evident at 0.55mg/kg/day (and above, as permitted by survival). Hyperostosis of the bones was observed, which was characterized by thickening of the cortical and trabecular bone. The thickening was endosteal and not periosteal, meaning that the bones became thicker through reduction of the diameter of the internal cavity. Increased thickness of cortical and trabecular bone resulted in decreased volume of marrow spaces, with consequent loss of marrow. There was no evidence of degeneration of the bone marrow that remained. Extramedullary hematopoiesis was observed in the liver and spleen; this may have occurred to compensate for the lost marrow. These observations (marrow reduction and extramedullary hematopoiesis) may account for the reduction in erythrocytes and increase in reticulocytes that were observed (see Hematology, above). Mineralization of certain soft tissues occurred, including the kidney, heart, and blood vessels. Although mild mineralization was observed in animals that received 0.06mg/kg/day or less, this was considered to be within normal limits for rats. Mineralization observed at 0.55mg/kg/day and above was more severe and was considered to be related to treatment. No remarkable microscopic observations were made in animals that received 0.06mg/kg/day or less (although, again, histopathology of these animals was limited to bone, bone marrow, spleen, liver, kidney, and heart).

Summary/conclusions: The primary treatment-related effects observed in this study included decreased survival (at the high dose), reduced body weight, elevated serum levels of calcium and phosphorus, reduced erythrocyte parameters, increased rates of excretion of calcium and phosphorus, increased mean kidney weight and decreased mean liver weight (females only), increased bone thickness, resulting in marrow loss, and mineralization of certain soft tissues. All of these effects are symptoms of excessive exposure to vitamin D, as would be expected. A dosage of 0.06mg/kg/day was considered to be a NOEL under the conditions of this study.

Reviewer's comment: *This study is inadequate to support a NDA for 1 α -OH-D₂ with respect to the need for toxicology data from a chronic rodent study. Histopathologic examination of all major tissues is a critical portion of a chronic toxicology study. The protocol for this study specified that histopathology (of tissues other than the bone, bone marrow, spleen, liver, kidney, and heart) be performed only on control and high-dose animals. Unfortunately, survival of the high-dose animals was extremely low. Only one high-dose male and seven high-dose females survived until the final week of the study. Therefore, this study effectively did not include histopathologic examination (except for the bone, bone marrow, spleen, liver, kidney, and heart). This is unacceptable. However, the clinical pathology data that were derived from this study are useable. In light of this, I believe that it would be acceptable for the sponsor to submit*

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histopathology data from a two-year rat bioassay in lieu of histopathology data from a six (or 12) month rodent study. In conjunction with the clinical pathology data from this study, our need for chronic rodent data would be satisfied. Data from the bioassay would presumably not be available until after long-term clinical studies had been conducted, but I believe that data from this study, from the one-year monkey study reviewed below, and from previous clinical studies (which have gone out to two years) would adequately support the safety of additional closely monitored clinical studies. It should also be noted that I was unable to locate the toxicokinetic data. The sponsor will be asked to respond to these matters.

2. One-year oral toxicity study in cynomolgus monkeys with [REDACTED] 870, study No. 295-135, in-life 8/91-8/92, study report dated 6/30/93, conducted by [REDACTED] in compliance with Good Laboratory Practice regulations (21 CFR 58).

1 α -OH-D₂ was dissolved in fractionated coconut oil and administered by gavage to groups of 5 young adult cynomolgus monkeys of each sex in dosages of 0 (vehicle control), 0.06, 0.6, 6, and 20mg/kg/day for one year. The dosages used in this study are compared to the maximum currently proposed clinical dosage (4mg/day, or 0.08mg/Kg/day in a 50kg individual) below:

Monkey dose (mg/kg/day)	Multiple of human dose (mg/kg basis)	Multiple of human dose (mg/m ² basis)
0.06	0.75x	0.26x
0.6	7.5x	2.6x
6	75x	26x
20	250x	88x

The parameters that were monitored included survival, clinical observations, body weight, food consumption, clinical pathology (blood chemistry, urinalysis, and hematology (including leukocyte differential)), ophthalmology, ECG, gross pathology (including organ weights), and histopathology. Clinical pathology was performed on samples obtained from all animals pretest and from all surviving animals after 1, 3, 6, 9, and 12 months on study. Blood samples were obtained from all surviving animals at 0, 2, 4, 6, 8, 12, and 24 hours after dosing during week 52 of the study; these samples were apparently analyzed to determine the plasma level of the test material, although those data do not seem to have been submitted. Histopathology was performed on all major tissues and gross lesions from all animals.

Results:

Survival. Of 5 animals/sex/group originally scheduled for terminal sacrifice, survival after 52 weeks was:

Dosage Level (mg/kg/day)	Number of Animals Surviving Until Week 52	
	Male	Female
0 (control)	5	5
0.06	5	5
0.6	5	5
6	3	5
20	4	1

Male animals at 6mg/kg/day were sacrificed *in extremis* during weeks 35 and 48 (both deaths were attributed to chronic interstitial nephritis). A male at 20mg/kg/day was found dead during week 21 (death was attributed to severe necrotic inflammation of the colon). Females at 20mg/kg/day were found dead

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during weeks 21 and 32 (deaths were attributed to chronic interstitial nephritis and pneumonia, respectively); females at 20mg/kg/day were sacrificed *in extremis* during weeks 35 and 37 (both deaths were attributed to chronic interstitial nephritis).

Clinical observations. Observations made of animals that eventually died (or were sacrificed *in extremis*) included decreased activity and appetite, emaciation, dehydration, hunched posture, ataxia, decreased defecation, diarrhea, discolored feces, and emesis. Animals at 6 or 20mg/kg/day that survived to scheduled sacrifice also exhibited decreased activity, decreased defecation, emaciation, and dehydration. Masses, observed on the hands, feet, face, or tail of two male and two female animals at 6mg/kg/day, were described as firm, white to yellow, raised, circular subcutaneous nodules. These masses were first noticed after between 6 and 12 months on study, and were considered to have been related to treatment.

Body weight. Animals (both male and female) at 6mg/kg/day and above did not gain weight as rapidly as did control animals, and in some instances lost weight. A dosage of 0.6mg/kg/day was a NOAEL for body weight.

Food consumption. Food consumption tended to decrease with increasing exposure to the test material.

Ophthalmology. No remarkable observations.

ECG. No remarkable observations.

Blood chemistry. No remarkable observations were made at 0.6mg/kg/day or below. At 6mg/kg/day and above, treatment-related observations in both males and females included trends toward increased levels of calcium, phosphorus (females only), and urea nitrogen, and, in females only, a reduction in the concentration of albumin.

Hematology. No remarkable observations were made at 0.6mg/kg/day or below. At 6mg/kg/day and above, both males and females exhibited trends toward decreased values of the concentrations of erythrocytes and hemoglobin and decreased hematocrit.

Urinalysis. No clear trends.

Organ weights. The mean absolute kidney weight tended to increase at 6mg/kg/day and above in both males and females; this observation correlated with microscopically observed mineralization and chronic interstitial nephritis of the kidney.

Gross pathology. As mentioned above under "clinical observations", some animals at 6mg/kg/day developed subcutaneous nodules. The nodules were found to contain creamy-yellow or tan-white viscous material. Similar, although less severe, nodules were observed on one control animal. These nodules made have resulted from mineralization of soft tissue in the subdermis, with subsequent inflammation and necrosis surrounding these foci. No other remarkable observations were reported.

Histopathology. Treatment-related microscopic changes were observed only at 6mg/kg/day and above, and included chronic interstitial nephritis, mild hyperostosis (increased thickness) of the ribs and sternum, and mild to severe mineralization of soft tissue of the foot, leg, and tail, the kidneys, blood vessels, the myocardium, the trachea, the lungs, the stomach, the ovary, and the uterus. In addition, mild to moderate degeneration of myocardial fibers was observed.

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Summary/conclusions: Treatment-related effects were largely confined to animals at 6mg/kg/day and above, and included decreased survival, reduced body weight gain and food consumption, elevated serum levels of calcium, phosphorus (females only), and urea nitrogen, reduced erythrocytic parameters, increased mean kidney weight, and mineralization of various tissues. All of these effects are symptoms of excessive exposure to vitamin D, as would be expected. A dosage of 0.6mg/kg/day was probably a NOEL under the conditions of this study.

Reviewer's comment: *The toxicokinetic data were apparently not submitted. The sponsor will be asked to submit these data if they are available.*

Previous Human Experience. Several clinical studies have been conducted with 1a-OH-D₂ under IND [REDACTED] including a study in which 28 postmenopausal osteoporosis patients received 2 to 5mg of 1a-OH-D₂ per day for one year, 20 of these subjects continued to receive the drug for an additional year. As expected, treatment with 1a-OH-D₂ induced mild to marked hypercalcemia and calciuria. The results of this study appear to support the safety of the clinical study proposed in submission 000 of IND [REDACTED]. Please see the Medical review for further details of the previous human experience with 1a-OH-D₂.

Summary/Discussion: The toxic effects observed following administration of the test material were the signs of excessive exposure to vitamin D. These effects included decreased survival, reduced food consumption and body weight gain, elevated serum levels of calcium and phosphorus, reduced erythrocyte parameters (apparently a consequence of increased bone thickness which resulted in decreased marrow volume), increased rates of excretion of calcium and phosphorus (especially in the rat), increased mean kidney weight, increased bone thickness, and mineralization of various soft tissues. Under the conditions of the one-year studies that were reviewed above, a dosage of 0.06mg/kg/day was considered to be a NOEL in the rat and a dosage of 0.6mg/kg/day was considered to be a NOEL in the cynomolgus monkey. The NOEL in the monkey was 7.5 times the maximum currently proposed human dose when compared on the basis of body weight, or 2.6 times the human dose following normalization to body surface area. As discussed above, the one-year rat study lacked definitive histopathology due to poor survival of the high-dosage group. However, taken in conjunction with other nonclinical and clinical data that have been reviewed under IND [REDACTED] (including a 13-week rat study that included histopathology of animals that received 2.5mg/kg/day), the available data adequately support the safety of the currently proposed clinical study.

Regulatory Conclusion: I have no objection to initiation of the proposed clinical study on the basis of pharmacologic or toxicologic concerns. Recommendations and comments indicated on the next page should be related to the sponsor.

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Recommendations to the Sponsor:

The following recommendations and requests pertain to IND [REDACTED]. All of the studies should be conducted in compliance with Good Laboratory Practice regulations (21 CFR 58). It is recommended that draft protocols for the nonclinical studies be submitted to the division for review prior to initiation of the studies to ensure compliance with current policies.

1. Appropriate assessment of the potential of 1a-OH-D₂ to induce carcinogenicity would be required to support a NDA for this compound. It is recommended that 1a-OH-D₂ be evaluated in carcinogenicity bioassays in two rodent species (preferably the rat and the mouse). The protocols for these studies, as well as supporting data (e.g., comparative toxicokinetic and metabolism data, the basis for dose selection, etc.), should be submitted to the division for review prior to initiation of the studies.
2. Please note that the one-year rat study that has been submitted (study No. 295-136, conducted by [REDACTED]) does not adequately support the need for chronic rodent toxicology data because (due to poor survival of high-dose animals) histopathology of a full range of tissues from treated animals that survived until the scheduled sacrifice was not performed. Data from an adequate chronic toxicology study conducted in rodents would be required to support a NDA for 1a-OH-D₂. However, in conjunction with data from study No. 295-136, histopathology data from an adequate carcinogenicity study conducted in rats would fulfill the need for chronic rodent toxicology data.
3. 1a-OH-D₂ should be assessed for potential to induce teratogenic effects in studies conducted in both a rodent species and a non-rodent mammalian species. These studies should be completed prior to initiation of clinical studies that involve large numbers of female subjects of childbearing potential.
4. A NDA for 1a-OH-D₂ should be supported by data from a study for effects on prenatal and postnatal development, including maternal function (section 4.1.2 of the ICH document entitled "Detection of Toxicity to Reproduction for Medicinal Products"). The rat would be the preferred species for this study.
5. 1a-OH-D₂ should be evaluated for potential to cause genetic toxicity *in vitro* in mammalian cell lines. It is recommended that a forward mutation study (e.g., a HGPRT/CHO study or a mouse lymphoma TK locus/L5178Y assay) and a chromosomal aberration study (in CHO cells) be performed. These assays should be completed prior to initiation of large scale clinical studies.
6. The one-year studies conducted in the rat (study No. 295-136) and the cynomolgus monkey (study No. 295-135) indicate that blood samples were obtained and (presumably) analyzed to measure the plasma levels of 1a-OH-D₂ and its metabolites. However, those data were apparently not submitted to IND [REDACTED]. Please submit those data, including appropriate pharmacokinetic analysis of the data.

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Norman A. See, Ph.D., R.Ph.
Reviewing Pharmacologist

cc:

IND: [REDACTED]

Serial No.: 000 and 001

HFD-540 Div. File

HFD-540/TOX/AJACOBS

HFD-540/PHARM/SEE

HFD-540/MO/O'CONNELL

HFD-540/CSOM/WHITE

HFD-345

Concurrence Only:

HFD-540/DD/JWILKIN

HFD-540/TOX/AJACOBS

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12/13/90

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December 13, 1990

Sponsor: Bone Care International, Madison, WI

Submission Date: November 29, 1990

Date Received: November 30, 1990

REVIEW OF PROPOSED PROTOCOL

Amendment Review

Drug: Hectorol; 1 α -OH-D₂; 1 α -hydroxyergocalciferol;
9,10-seco(5Z,7E,22E)-5,7,10 (19), 22-ergostatetraene-1 α ,3B-diol

Category: Vitamin D₂ synthetic analog

Proposed Clinical Indication: Postmenopausal osteoporosis

Protocol: 52 wk oral toxicity study in [REDACTED] CD rats #295-136
Each group will contain 25/sex. Proposed dose levels for this study are 0.02, 0.06, 0.39 and 2.5 ug/kg/day. The vehicle is fractionated coconut oil. The basic design of this chronic study is adequate. There is some concern over the proposed dose levels. The dose selection by the sponsor is based on a 13 wk toxicity study in rats.

Doses of Hectorol used in the 13 wk study were 0.06, 0.39 and 2.5 ug/kg/day (approximately 0.8, 5 and 31x the clinical dose). Only a single male from the low and high dose groups each, died during the course of the study. The body weight decrease in the high dose group was significant, but it was <10%. Although tubular micro-concretions were present in all groups, the incidence of this lesion was dose related.

It is presumed that Hectorol is converted to 1,25(OH)₂D₂ (biologically active form) in the liver. Thus a comparison to toxicities of 1,25(OH)₂D₃ may be made. It should be kept in mind that 1,25(OH)₂D₃ is more potent than Hectorol. Toxicity studies (6-month) with 1,25(OH)₂D₃ (IND 11,818) in rats and dogs have noted soft tissue calcification, in addition to the presence of renal calculi. Osseous changes included bone resorption with fibrous tissue replacement, as well as altered structure of the epiphyseal plate.

With the limited effects of Hectorol observed in 13-wk studies in rats and monkeys; and the limited dose range used (same dose range tested in both species) it is difficult to assess the potential toxicities of this compound. Thus it is recommended that a 5.0 ug/kg/day dose level be included in this protocol.

Determination of serum levels of Hectorol (probably 1,25(OH)₂D₂) should be conducted.

Recommendation: The 52-wk toxicity study may be initiated with the following requested modifications to be conveyed to the sponsor:

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1. It is suggested that a 5.0 ug/kg/day group be included in the protocol. A lower dose group may be deleted at the sponsor's discretion.
2. Blood levels of the test drug (steady state levels) should be determined.

/S/

Chhanda Dutta, Ph.D.

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CC: HFD-510, HFD-345
HFD-510/A Jordan/C Dutta

12/18/90

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October 24, 1990

Sponsor: Bone Care International, Madison, WI

Submission Date: October 12, 1990

Date Received: October 18, 1990

REVIEW AND EVALUATION OF TOXICOLOGY DATA

Amendment Review

Drug: Hectorol; 1 α -OH-D₂; 1 α -hydroxyergocalciferol;
9,10-seco(5Z,7E,22E)-5,7,10 (19),22-ergostatetraene-1 α ,3B-diol

Category: Vitamin D₂ synthetic analog

Proposed clinical indication: Treatment of postmenopausal osteoporosis. A protocol change in study H-102 was included with this submission. Originally, the objective of this Phase I study was to examine extended treatment (4 wks) with a constant dosage of 1 α -OH-D₂ in postmenopausal patients. The length of treatment was then increased to 52 wks, with a dose of 4 ug/day. The current protocol change will further extend the treatment period to 104 wks.

13 wk Study in Cynomolgus Monkeys #615-004

Three groups of monkeys (4/sex/group) were given 0.06, 0.39 and 2.5 ug/kg/day of 1 α -OH-D₂, by oral gavage. Control group received vehicle (fractionated coconut oil).

Observed Effects

Diarrhea and emesis were noted only in the treated animals. A higher incidence of alopecia was noted in the treatment groups, but a dose relationship was not evident.

Body Weight and Food Consumption

Mean body weights of high dose males and females were slightly decreased throughout the study. Food consumption data was not provided.

Hematology

Treatment related changes in hematological parameters were not found.

Clinical Chemistry

Significantly elevated serum phosphorus levels were noted in the low and middle dose males. This effect was not dose related. In treated females, serum phosphorus levels were similar to control values. Significantly elevated urea nitrogen was noted only in low dose females during month 2 of the study. Changes in serum albumin were also found in the low dose group. Although these changes were significant, a dose effect was not present. Since the changes in clinical chemistry occurred sporadically,

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toxicological significance (if any) cannot be determined from these data.

Urinalysis

The results of the urinalysis were confounded by possible "water contamination". Urinary calcium and phosphorus levels were not indicated in the summary tables. However, the sponsor did state that a >25-fold increase in urinary calcium and a 3 to 9-fold reduction in urinary phosphorus occurred in control animals. Basically these data were limited and meaningless.

Organ Weights

Significantly increased relative weights of pituitary and ovary were found only in the middle dose females. Treatment related changes were not found.

Gross Pathology

High dose males were noted to have excess fat or white focus in the heart. Both lesions were of mild severity. Adhesions and tan foci in the liver were noted only in low and high dose males. Enlargement (mild) of tracheobronchial, mandibular and mesenteric lymph nodes were observed in low dose males and high dose monkeys. These lesions were considered to be incidental.

Histopathology

Chronic interstitial nephritis (trace) was noted in all groups. Cyst in the parathyroid gland was noted in one middle dose female and in one high dose male. The lesions noted were of isolated incidence and thus did not reflect treatment effects.

Summary: A 13 wk toxicity study was conducted in *Cynomolgus* monkeys. Doses used were 0.06, 0.39 and 2.5 ug/kg/day (0.75, 5 and 31x HD). Frank toxicity of 1 α -OH-D₂ was not demonstrated in this study. Since data on blood levels of drug and its pharmacokinetics in monkeys were not provided in this submission; it is unclear as to whether the monkey is an appropriate model for toxicity studies with 1 α -OH-D₂.

A previously reviewed 13 wk study in rats also used 0.06, 0.30 and 2.5 ug/kg/day of 1 α -OH-D₂. Treatment with the middle and high doses resulted in weight loss, elevated serum calcium and phosphorus; and elevated urinary calcium and phosphorus. Renal tubular micro-concretions and pelvic calculi were noted as dose related lesions. Minimal toxicity was found with 0.06 ug/kg/day (0.75x HD).

Calcification of renal tubules has been observed with other vitamin D compounds. In 6 month toxicity studies with 1,25(OH)₂D₃ (IND [redacted]), elevated serum calcium and phosphorus levels were found in both rats and dogs. Furthermore, calcification of renal tubules occurred in both species. Doses used in both the rat and dog studies were 0.02, 0.08 and 0.3 ug/kg/day (0.5-7.5x HD). On the other hand, 3-12 ug/kg/day (0.8-3x HD) of 25-OH-D₃ (IND 9881) for 6 months was found to be non toxic in dogs. In a 6 month

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study in rats, calcification of renal tubules and urinary calculi were found with 40 ug/kg/day (10x HD).

The sponsor has indicated that 2 protocols for toxicity studies (prior to Phase III) will be submitted in the future. The proposed animal models include Sprague-Dawley rats and Cynomolgus monkeys. In consideration of the minimal toxicity observed in the 13 wk monkey study and with our limited experience in evaluating vitamin D compounds in this species; the canine model may be an alternative. Pharmacokinetic data of 1 α -OH-D₂ has been obtained only in Cynomolgus monkeys. Determination of appropriate animal models for future toxicity studies will have to await review of the monkey pharmacokinetic data.

Recommendation: Under normal circumstances, data from 13 wk toxicity studies would be insufficient to support 104 wk clinical trial. Since clinical protocol H-102 is an ongoing study and renal parameters are being closely monitored, the extension to 104 wks will be reasonably safe.

The following comments should be conveyed to the sponsor:

1. Data on the blood levels of 1 α -OH-D₂ attained in the 13 wk study in monkeys would allow a thorough evaluation of this study. Please submit such data (if available) for our consideration.
2. At the current time, pharmacokinetic data of 1 α -OH-D₂ in animals is scarce. The timely submission of the final report of pharmacokinetic study in Cynomolgus monkeys would be pertinent.

/S/

Chhanda Dutta, Ph.D.

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CC: IND, HFD-510, HFD-345
HFD-510/A Jordan/C Dutta

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C. P. Miller

JUN 6 1990
JUN 8 1990 June 6, 1990

Sponsor: Bone Care International., Madison, WI 53713

Submission Date: April 16, 1990

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Amendment ReviewDrug: HECTOROL, (9,10-seco(5Z,7E,22E)-5,7,10(19),22 ergostatetraene-1a,3B-diol), (1a-OH-D₂)Category: Vitamin D₂ synthetic analogue

Date of previous pharmacology review: 4/15/88

Proposed clinical indication: This vitamin D compound is proposed to be used in the treatment of osteoporosis. Phase I study was initiated prior to completion of required toxicity studies. Phase I study was allowed to proceed based upon a 13 wk oral toxicity study in male Sprague-Dawley rats. There are four studies composing the Phase I study:

- A. H-101: Dose ranging.
- B. H-102: Extended dosing at constant dosage.
- C. H-103: Conversion to 1,25D₂
- D. H-104: Pharmacokinetic

The dose ranging study (7 weeks) has been completed. Postmenopausal osteoporotic patients received 0.5 mcg/day for the first week and then successively higher doses of 1.0, 2.0, 4.0, 5.0, 8.0 and 10.0 mcg/day during the subsequent six weeks. Mild hypercalciuria was reported at the higher doses but serum calcium levels were within normal range. Study H-102 was originally proposed to examine the long term (4 wks) effects of 1a-OH-D₂. This protocol was changed and the treatment period has been extended to 52 weeks. In this study, patients receive progressively increasing doses of 2.0, 3.0, 4.0, and 5.0 mcg/day with one week of treatment at each level. Once the maximum dose has been achieved, it will be maintained for the duration of the study. This study is currently in progress and considered to be a Phase I study despite the 52 week duration. Additionally, a tentative protocol for the pharmacokinetic study has been discussed (March 1990) and submission of a formal protocol is pending.

Acute oral toxicity study in rats #615-001. (Drug lot #K002) Study was conducted at [redacted]. Each group of rats (5 males and 5 females) was given a single oral dose of 1a-OH-D₂ by gavage. The 1a-OH-D₂ was prepared (v/v) in fractionated coconut oil and administered at doses 1.25, 2.5, 5.0 and 10.0 mg/kg. A vehicle control group was not included.

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Mortality and LD₅₀ The LD₅₀ values reported were 1.7 mg/kg and 1.8 mg/kg for males and females, respectively. Data on mortality is summarized below.

<u>Dose (mg/kg)</u>	<u>Mortality (%)</u>	
	M	F
1.25	40	0
2.5	60	100
5.0	100	100
10.0	100	100

Observed effects Rats that received 1.25 - 5.0 mg/kg of 1a-OH-D₂ had soft stool or diarrhea following administration of the drug (Day 1). The rats were observed to decline in activity at all the doses used. However the onset of lethargy was delayed (4-7 days post dosing) in the rats administered 1.25 and 2.5 mg/kg. Additionally, some of these rats exhibited tremors, ataxia, discoloration around the mouth or nose and constipation during a period 4-9 days post dosing.

Body weight and food consumption Body weights were measured on days 0, 8 and 15 of the study. In comparison to Day 0, rats in all the treatment groups displayed a loss in body weight (7-21%) on Day 8 of the study. Rats receiving the lowest dose of 1a-OH-D₂ exhibited a gain in body weight by Day 15. Animals in the other treatment groups did not survive until Day 15. No data was provided for food consumption.

Gross pathology In all the treatment groups, animals dying during the course of the study were found to have discoloration of the kidney and congestion of the glandular mucosa of the stomach. Tan foci on the heart was also present in these animals except those dosed with 5.0 mg/kg. Lung congestion was also found in some of the animals.

In those animals sacrificed at the end of the study, white foci on the serosal surface of the stomach was present in the 1.25 and 2.5 mg/kg groups. Two males from the 2.5 mg/kg group were found to have red foci on the lung.

13 Week oral toxicity study in rats #615-002. (Drug lot #K003) Four groups of rats (15 males and 15 females/group) were administered 1a-OH-D₂ orally, by gavage. In addition to a control group receiving only vehicle (fractionated coconut oil), the doses of 1a-OH-D₂ tested were 0.06, 0.39 and 2.5 mcg/kg/day. The doses being used in the 52 wk Phase I study are from 0.04-0.1 mcg/kg/day.

Mortality During the course of the study, there were two deaths. One male died from both the 0.06 and 2.5 mcg/kg/day groups. The male from the low dose group died on Day 32 as a result of injury suffered during intubation. The other male animal in the high dose group died on Day 85 and experienced difficulty in breathing, decreased defecation and had yellow

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staining on the anogenital region prior to death. This death was attributed to the test drug.

Body weight and food consumption Animals in the 2.5 mcg/kg/day group consistently had lower body weights than control animals, from wk1 to wk13 of the study. This difference in body weight was statistically significant during wks 8 to 13. Female rats receiving 0.39 and 2.5 mcg/kg/day had lower (<10%) body weights than control female rats throughout the 13 weeks. Females in the high dose group showed a 8.2% decrease in body weight, which was statistically significant.

In general, the middle and high dose levels resulted in decreased food consumption in comparison to control. During the first four weeks, food consumption was found to be significantly lower than control in males given 0.39 and 2.5 mcg/kg/day of 1 α -OH-D₂. Males in the high dose group also had significantly lower food consumption in the final 2 weeks of the study. Females in the middle and high dose groups had significantly lower food consumption during weeks 2 and 3.

Hematology There were no differences in these parameters between the treatment groups.

Clinical Chemistry Serum phosphorus levels were significantly elevated in the males at the middle dose and in both males and females at the high dose. Significant increase in serum calcium was observed only in the males of the high dose group.

Urinalysis Urinary calcium, urinary phosphorus and their ratios to creatinine were all elevated, in the middle and high dose groups.

Ophthalmic Examination All animals were examined prior to the study and were found to be normal. After 13 wks, the rats were examined again. Two control animals were found to have choroidal hypoplasia in the right eye only. This finding was attributed to the age and the strain of rats used in this study. In the low dose group, one animal exhibited unilateral (right eye) choroidal hypoplasia also. Retinal atrophy and choroidal hypoplasia were present in the rats receiving the highest dose. Of the five animals affected in this group, four were males. Additionally, the ophthalmic abnormalities were present both unilaterally and bilaterally. Such pathologies in the high dose group were attributed to the test drug.

Organ Weights An increase in adrenal weights was found in the animals in the 2.5 mcg/kg/day group and was thought to be stress related. Animals in this dose group also showed a decrease in kidney and heart weights. These increases in organ weights were not associated with pathologies. Other changes observed were an increase in the brain weight of males in the high dose group and an increase in ovarian weights of females in the middle dose group. Although these latter

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changes were statistically significant, the sponsor considered it to be of little importance.

Gross Pathology Some control animals exhibited discoloration of the lung, enlargement of mandibular lymph nodes, nodules or cysts in the skin of the ear, hydronephrosis and calculi in the urinary bladder. At all three doses of the drug, one male from each group was found to contain calculi in the kidney or urinary bladder. This lesion was attributed to the test drug.

Histopathology Following microscopic examination, 11 male and 12 female rats each, from the middle and high dose groups were found to have renal pelvic calculi. This lesion was graded as severe only in the animals of the high dose group. Renal tubular microcretions were evident in control and treatment groups. The higher incidence of this lesion in the treatment groups was dose related (27% with middle dose and 86% with high dose).

Summary and evaluation The acute toxicity study examined the effects of 1.25, 2.5, 5.0 and 10.0 mg/kg of 1a-OH-D₂. The middle and high doses tested resulted in congestion of the stomach and subsequent death.

The 13 week toxicity study in rats, examined the effects of 0.06, 0.39 and 2.5 mcg/kg/day doses of 1a-OH-D₂. It is noted that the animals were maintained on a complete diet. Thus the fold differences in the doses of the test drug will be different. The 0.39 and 2.5 mcg/kg/day doses resulted in decreased body weights, elevated serum calcium and phosphorus levels and elevated urinary calcium and phosphorus. Dose related lesions included renal tubular microcretions and pelvic calculi. Minimal toxicity was observed with the 0.06 mcg/kg/day dose.

Recommendation This toxicity study is partial fulfillment of the studies required prior to Phase I studies. A second 13 wk oral toxicity study is being conducted in cynomolgus monkeys. At the present time there is little animal pharmacokinetic data available. The sponsor has conducted some preliminary pharmacokinetic studies in the monkey model. The sponsor should be requested to submit such data along with the toxicology data in the cynomolgus monkey, since the Phase I studies have been initiated. Detailed information about chromatographic techniques utilized to discern vitamin D₂ metabolites from vitamin D₃ in the pharmacokinetic studies should also be included.

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Chhanda Dutta, Ph.D.

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CC: IND, HFD-510, HFD-345
HFD-502/Weissinger
HFD-510/A Jordan/C Dutta

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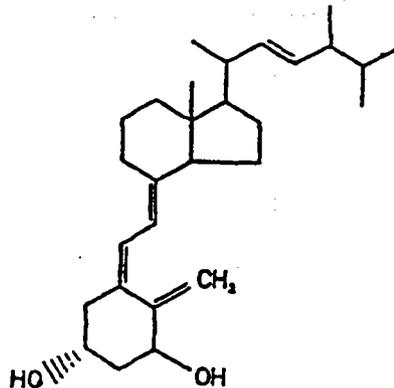
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 Bone Care International, Incorporated
 Madison, WI
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Review and Evaluation of Pharmacology and Toxicology Data
 Original Summary

Drug: Hectorol (1-alpha-hydroxyvitamin D₂, 1a-OH-D₂)



Category: Vitamin D hormone

Proposed Clinical Investigation:

Objectives:

1. To determine the optimal safe and effective dosage of 1a-OH-D₂ for postmenopausal osteoporotic patients with regard to serum and urine levels of calcium.
2. To investigate the effect of increasing doses of 1a-OH-D₂ on bone formation, as evidenced by serum levels of osteocalcin.
3. To examine the safety of increasing doses of 1a-OH-D₂ on kidney function, as determined by creatinine clearance and blood levels of urea nitrogen.
4. To monitor changes in the serum levels of 25-hydroxyvitamin D, 1a, 25-dihydroxyvitamin D and 1a-hydroxyvitamin D₂ with escalating doses of 1a-OH-D₂.

Clinical Protocol: Twenty postmenopausal patients. the drug will be given initially at 0.5 ug/day for the first week, and at successively higher doses of 1, 2, 4 and 5 ug/day in each of the following four weeks.

Preclinical Animal Studies:

Pharmacology: Information given by the sponsor from published literatures:

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Metabolism and Functions of Vitamins D₂ and D₃:

Vitamins D₂ and D₃ are activated in identical fashion to potent hormones in both birds and mammals. Vitamin D₃ is hydroxylated by the liver to form 25-hydroxyvitamin D₃ and further hydroxylated at the 1-alpha position by the kidney to form 1a,25-dihydroxyvitamin D₃. Vitamin D₂ is similarly hydroxylated to form 25-hydroxyvitamin D₂ and then 1a,25-dihydroxyvitamin D₂. The end products formed are the most potent hormones derived from either vitamin

Both 1a,25-dihydroxyvitamin D₃ and 1a,25-dihydroxyvitamin D₂ precisely regulate blood calcium at levels required for essential body functions, including normal bone growth. Specifically, these hormones control the intestinal absorption of dietary calcium, the conservation of calcium by the kidney, and, if necessary, the mobilization of calcium from the skeleton. Both may act directly on bone cells to stimulate skeletal growth, but conclusive evidence is presently lacking.

The two vitamin D hormones accomplish their functions by interacting with highly specific receptor proteins in the small intestine, kidney, parathyroid gland, bone and other target tissues. Limited biological testing indicates that both hormones have approximately equal activities, as judged by antirachitic line tests in rats and binding to the intestinal receptor protein in chicks. The apparent activity of the vitamin D₂ hormone in chicks, however, is approximately 5 to 10 times lower, probably due to its more rapid inactivation in this species.

Both 1a,25-dihydroxyvitamin D₂ and 1a,25-dihydroxyvitamin D₃ are presumed to undergo similar metabolic deactivation and excretion. The vitamin D₃ hormone is known to be rapidly deactivated by conversion to calcitroic acid and ultimately to breakdown products excreted via the biliary route. Similar deactivation and excretion of the vitamin D₂ hormone has not yet been confirmed.

Two vitamin D analogues have been discovered which have high biological activities. One of these analogues, 1a-hydroxyvitamin D₃ (1a-OH-D₃) is rapidly converted by the liver to 1a,25-dihydroxyvitamin D₃ when administered to rats, chicks and man. This conversion is so rapid that 1a-OH-D₃ is probably metabolized to the native hormone before functioning in its target tissues. Intravenous administration of ³H-1a-OH-D₃ to man allows the detection of ³H-1a, 25-dihydroxyvitamin D₃ within 30 minutes and maximum serum levels of the tritiated hormone by twelve hours. Oral administration of 4 ug of non-radiolabeled 1a-OH-D₃ to man also causes peak serum levels of 1a,25-dihydroxyvitamin D₃ of approximately 70 pg/ml by 10-12 hours. In the latter case, serum levels of the vitamin D₃ hormone return to normal within 48 hours.

The second analogue, 1a-OH-D₂, is presumed to be converted in similar fashion to 1a,25-dihydroxyvitamin D₂, but confirmation is not currently available. Evidence which points to this conversion is available from comparisons of the biological activities of 1a-OH-D₂ and 1a-OH-D₃. When 1a-OH-D₂ is administered to rachitic rats, it elicits increases in intestinal calcium transport and bone mobilization which are similar in

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magnitude and duration to those elicited in comparable studies of 1 α -OH-D₃. When directly compared in the same experiment, the two analogues are approximately equal in their abilities to increase intestinal calcium absorption, serum calcium levels, and epiphyseal plate calcification in rachitic rats.

Toxicity:

One study has been completed to date which examined the acute oral toxicity and sub-chronic oral toxicity of 1 α -OH-D₂ in male rats. This study was conducted by Drs. G. Sjoden and H. F. Deluca at University of Wisconsin and has been published (Proceedings of the Society for Experimental Biology and Medicine 178: 432, 1985).

The study was designed to compare the relative toxicities of 1 α -OH-D₂ and 1 α -OH-D₃ in 200 g (6-7 week) Holtzman rats. To determine acute toxicities, eight groups of 6 rats were administered varying doses of either compound (by gavage) and monitored for 14 days. The median lethal dose for 1 α -OH-D₂ was estimated to be 3.5 mg/kg, while that for 1 α -OH-D₃ was estimated to be 0.2 mg/kg. Based on these data, 1 α -OH-D₂ is approximately 15 times less toxic than 1 α -OH-D₃.

To determine sub-chronic toxicities, six groups of 6 rats were orally administered 2.5, 5 and 20 μ g/kg/day of 1 α -OH-D₂ or 1 α -OH-D₃ for 4 weeks. Two deaths were observed with 1 α -OH-D₂, both occurring during the fourth week at the highest dose level. By comparison, seven deaths were observed with 1 α -OH-D₃. Two of these deaths occurred during the third and fourth weeks at the intermediate dose level. The remaining five deaths occurred at regular intervals at the highest dose. As 20 μ g/kg/day of 1 α -OH-D₂ caused the same mortality as 5 μ g/kg/day of 1 α -OH-D₃, the vitamin D₂ analogue is approximately 4 times less toxic than the vitamin D₃ analogue.

The observed changes in body weight and serum calcium levels support the lower sub-chronic toxicity of 1 α -OH-D₂. Rats dosed with 1 α -OH-D₂ and 1 α -OH-D₃ gained less weight than controls. However, rats administered 2.5 or 5 μ g/kg/day of 1 α -OH-D₂ gained more than 75 % of the weight gained by controls while rats receiving comparable doses of 1 α -OH-D₃ showed marginal weight gain or weight loss. Rats dosed with 20 μ g/kg/day of either compound showed equivalent weight losses. Hypercalcemia was observed in all rats treated with either compound, but was less severe at all times in rats treated with 1 α -OH-D₂.

Post-sacrifice kidney analyses showed that increasing doses of either vitamin D analogue caused corresponding increases in kidney calcium content. However, the increases observed from 1 α -OH-D₂ were significantly lower than those from 1 α -OH-D₃.

Comments: Two drugs are presently indicated for treating osteoporosis, namely estrogen and calcitonin. These drugs are anti-resorptive agents and are ineffective in stimulating new bone growth. Estrogen replacement therapy, while effective in arresting postmenopausal bone loss, is not yet widely accepted because of undesirable side effects. Calcitonin therapy has limited

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acceptance due to its required parenteral route of administration and its short-term effectiveness.

Over-the counter calcium supplements also are available for treating osteoporosis. Recent evidence concludes that calcium supplements inhibit bone resorption without affecting bone formation, thereby slowing bone loss. Little evidence suggests that calcium supplementation actually restores positive calcium balance in osteoporotic patients, probably because calcium absorption is commonly impaired in this disorder.

Low serum levels of 1 α -25-dihydroxyvitamin D₃ have been documented as secondary characteristics of both type I (postmenopausal) and type II (senile) osteoporosis. In both disorders, the reduction in serum 1 α ,25-dihydroxyvitamin D₃ is caused by insufficient renal 1 α -hydroxylase activity. In type I osteoporosis, the 1 α -hydroxylase is indirectly suppressed by postmenopausal estrogen deficiency. In type II osteoporosis, the enzyme is impaired.

Insufficient production of 1 α ,25-dihydroxyvitamin D₃ predisposes an individual to develop osteoporosis. By an indirect mechanism, low serum levels of 1 α ,25-dihydroxyvitamin D₃ cause inadequate intestinal calcium absorption and trigger the secretion of PTH. Elevation of serum PTH increases the rate of bone remodeling and in the absence of adequate bone formation, decreases bone mass. Prolonged loss of bone, over time, leads to osteoporosis. By a possible direct mechanism, low production of 1 α ,25-dihydroxyvitamin D₃ prevents delivery of adequate hormone to the bone tissue itself, thereby interrupting normal bone formation.

The central etiological role of 1 α ,25-dihydroxyvitamin D₃ in osteoporosis has prompted many clinical investigations of the hormone as a potential osteoporosis treatment. Some of these early clinical studies have found that 1 α ,25-dihydroxyvitamin D₃ increases or stabilizes bone mass and the others have not. Subsequent studies have found that the vitamin must be administered at dose levels above 0.6 μ g/day in order to stabilize bone mass. Higher dosages are required for bone growth.

Unfortunately, calcitriol often causes hypercalciuria and secondarily hypercalcemia when administered at doses above 0.6 μ g/day. Calcitriol doses of 0.5- 1 μ g/day cause hypercalciuria if a patient's daily calcium intake is normal (about 800 to 1000 mg). The dosage can be increased to 2 μ g/day only if the calcium intake is restricted to less than 600 mg. Clearly higher doses would require impractical dietary restrictions. The side effects of oral calcitriol therapy are caused by hyperabsorption of dietary calcium-not bone resorption.

The risk of hyperabsorption of calcium can be lowered by administering calcitriol i.v. or by orally administering 1 α -hydroxylated vitamin D analogues. These analogues, namely 1 α -hydroxyvitamin D₃ and 1 α -hydroxyvitamin D₂, are relatively ineffective in stimulating calcium absorption until they are hydroxylated at the 25 position by the liver. As a result, these analogues offer two key advantages over calcitriol for osteoporosis: first higher dosages of the analogues can be orally

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administered before hypercalciuria is observed; and second, less drug is lost to the intestine, and more is ultimately delivered to the bone. The effectiveness of la-hydroxyvitamin D₃ has been demonstrated. The drug produced dose-dependent increases in bone mineral content in postmenopausal osteoporotic women. However transient hypercalcemia was still observed in few patients.

Evidence of the effectiveness of la-hydroxyvitamin D₂ in treating osteoporosis is still lacking. The sponsor speculates that la-OH-D₂ is as effective as la-OH-D₃ in stimulating bone growth. Evidence which supports the postulation comes from comparisons of biological activities of la-OH-D₂ and la-OH-D₃. When la-OH-D₂ is administered to rachitic rats, it elicits increases in intestinal calcium transport and bone mobilization which are comparable in magnitude and duration to those elicited by la-OH-D₃. The two analogues are also approximately equal in their abilities to increase epiphyseal plate calcification in rachitic rats.

The submitted toxicity studies are adequate to support the planned Phase I clinical investigation. Phase II 90-day toxicity studies in rats and dogs will be required.

Six month toxicity studies in rats and dogs must be done before Phase III trials are initiated. Carcinogenicity studies will not be necessary for this compound. *P. ... studies will only be necessary if the drug is to be used in patients with reproductive potential.*
Recommendation: To allow to proceed.

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I. Huang, Ph. D.

CC: Orig IND, HFN-010, HFN-010/*A Jordan* ~~Pharmacology~~, HFN-010/Huang

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